UNITED STATES PATENT AND TRADEMARK OFFICE

C 1C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,640	03/05/2002	James D. Marks	407T-897221US	1369

22798 7590 09/27/2005

QUINE INTELLECTUAL PROPERTY LAW GROUP, P.C.
P O BOX 458
ALAMEDA, CA 94501

EXAMINER	
SANG, HONG	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,640	MARKS ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *34-39 and 48-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *21-28,42 and 45* is/are rejected.

7)☒ Claim(s) *27,46 and 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

8.00

DETAILED ACTION

RE: Marks et al.

1. The examiner of your application in the PTO has changed. To aid in correlating of any papers for this application, all further correspondence regarding this application should be directed to Hong Sang, Art Unit: 1643.

2. Applicant's election of Group I (Claims 21-28, 41, and 45-47) in the reply filed on 6/17/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. The information disclosure statement (IDS) filed on 1/7/2003 has been considered. A signed copy is attached hereto.

4. Claims 1-50 are currently pending. Claims 1-20, 29-33, 40, and 42-44 are cancelled without prejudice in the preliminary amendment filed on 3/5/02. Claims 34-39, 48-50 are withdrawn from further consideration as being drawn to nonelected inventions.

5. Claims 21-28, 41 and 45-47 are under examination.

Specification

6. The first line of the specification should be updated if applicant desires priority under 35 U.S.C. 1 19(e), 120, 121 and 3654c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the

relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application (s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No.___" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date 6f the parent application.

For additional information, see United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application". Appropriate correction is required.

Claim Objections

7. Claims 46 and 47 are objected to because they are duplicates of Claim 45. Appropriate correction is required.

8. Claim 27 is objected to because the word "the" is duplicated. Appropriate correction is required.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claim 21, and its dependent claims 22-27, Claim 41 and its dependent claims 45-47 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter

Claims 21, 41 and their dependent claim 22-27, 45-47 as written, do not sufficiently distinguish over nucleic acids as they exists naturally because claims do not particularly point out any non-naturally occurring differences between the claimed nucleic acids and naturally occurring nucleic acids.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" nucleic acids or similar language would obviate this rejection.

Claim Rejections - 35 USC § 112, 2nd paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 21 and its dependent claims 22-27, claim 28, claims 41 and its dependent claims 45-47 are rejected as vague and indefinite for reciting the term "C6 antibody" and "C6.5 antibody" as the sole means of identifying the claimed molecule. The use of

laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify "C6 antibody" and "C6.5 antibody", for example, by SEQ ID NO. or deposit of the hybridoma producing the "C6 antibody" and "C6.5 antibody".

Claim Rejections - 35 USC § 112, 1st paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claim 28 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants broadly claim a cell comprising a recombinant nucleic acid that encodes a human antibody that specifically binds c-erbB-2. These claims read on a cell within a transgenic animal given that the term "isolated" is not denoted in describing the cell.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. For example, Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that

within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). The art of transgenic animals has for many years stated that the unpredictability lies, in part, with the site or sites of transgene integration into the target genome and that "the position effect" as well as unidentified control elements are recognized to cause aberrant expression of a transgene (Wall, 1996 Theriogenology, Vol. 45, pp. 57-68). The elements of the particular construct used to make transgenic animals are also held to be critical, and they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc. (Houdebine, 1994, J. Biotech. Vol. 34, pages 269-287, specifically page 281). Furthermore, transgenic animals are regarded to have within their cells, cellular mechanisms that prevent expression of the transgene, such as methylation or deletion from the genome (Kappell, 1992, Current Opinions in Biotechnology, Vol. 3, pp. 548-553).

Well-regulated transgene expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron, 1997, Mol. Biol. 7, pages 253-265, specifically page 256, col. 1 -2, bridge. paragraph). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron, 1997, Mol. Biol. 7, page 256, lines 3-9). With regard to the importance of promoter selection, Niemann (1997) states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate

phenotypes - one deleterious to the pig, the other compatible with pig health (Niemann, 1997, Transg. Res. 7, pages 73-75, specifically page 73, col. 2, parag. 2, line 12 to page 73, col. 1, line 4).

Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. Mullins (1993, Hypertension, Vol. 22, pp. 630-633) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describes spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023). Mullins (1996, J. Clin. Invest. Vol. 98, pages S37-S40) disclose that the use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another. Thus, at the time of

filing, the phenotype of a transgenic cell contained within any animal was unpredictable and could not be prepared for any species. Applicants can obviate the instant rejection by amending the claims to recite the term "isolated" before the recitation, "cell".

15. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 23 is drawn in part to a nucleic acid encodes an antibody having a V_L or V_H CDR3 domain.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions,

particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that antibody having a V_L or V_H CDR3 as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an C6 antibody have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Further, the specification does not teach that a functional human antibody having a V_H and V_L CDR3. As evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity.

In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

One of skill in the art would neither expect nor predict the appropriate functioning of the antibody as broadly as is claimed. It is suggested that the specific portion of the human constant region, which the variable region is covalently linked to, be explicitly recited within the claim or this language be removed completely in order to obviate this rejection. Therefore, in view of the lack of guidance in the specification and in view of

the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

17. Claims 21-22, 24-28, 41, 45-47 are rejected under 35 U.S.C. 102(a) as being anticipated by Schier et al. (Immunotechnology 1:73-81, 1995).

Claims 21-22, 24-28, 41, 45-47 are drawn to a nucleic acid encoding a human C6 antibody that specifically binds to c-erbB-2; a cell comprising a recombinant nucleic acid that encodes a human antibody that specifically binds C-erbB-2; a nucleic acid molecule comprising a nucleotide sequence encoding a single chain polypeptide that exhibits the antibody-binding specificity of a human C6 antibody; an expression cassette comprising the said nucleic acid; the claims are further limited to a nucleic acid encodes the variable light (V_L) chain of C6.5, a variable heavy (V_H) chain of C6.5, C6.5, the amino acid of a C6.5 antibody and conservative amino acid substitutions of said C6.5.

Schier et al. teach a human C6.5 antibody and a human single-chain Fv (C6.5) which bind specifically to C-erbB-2 (see entire document). Schier et al teach using phage display of antibody gene repertoires to produce human sFv (C6.5) (see abstract, lines 3-4) and the library was created from a repertoire of sFv genes consisting of

human heavy and light chain variable region (V_L and V_H) genes isolated from the peripheral blood lymphocytes of unimmunized human volunteers (see page 74, right column, 2nd paragraph, lines 3-7). Schier et al teach C6.5 binds to immobilized c-erbB-2 extracellular domain with a K_d of 1.6x 10^{-8} M and to c-erB-2 on SK-OV-3 cells with a K_d of 2.0x 10^{-8} M, an affinity that is similar to sFv produced against the same antigen from hybridomas (see abstract, lines 8-12). Schier further teaches that C6.5 sFv gene was subcloned into the expression vector PUC119Sfi1/Not1Hismyc, which was used to transfect E.coli HB2151 cells (see page 75, right column, 2nd paragraph, lines 1-3, 14-15). Furthermore, although not explicitly taught, in the absence of evidence to the contrary, the C6.5 antibody taught by Schier et al. would be the same as claimed C6 antibody. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 21-22, 28, 41, 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over US patent NO: 6,165,464 (earliest filing date is at least 1/25/1988) in combination of the teaching of Wels et al. (J. Steroid Biochem. Mol. Biol. 43 (1-3): 1-7) and Marks et al. (Biotechnology 10: 779-783, 1992, IDS).

The claims limitations are set forth above (see paragraph 17).

US patent NO: 6,165,464 teaches an isolated human antibody which specifically binds to HER2 receptor and a human hybridoma producing a human antibody which specifically binds to HER2 receptor (see Claims 1 and 10). US patent NO: 6,165,464 teaches a method of inhibiting growth of tumor cells by treatment of the cells with said antibodies, which inhibit the growth factor receptor function (see abstract). US patent NO: 6,165,464 does not teach the nucleic acids encoding single chain antibody, or the variable light or heavy chain of the antibody.

Wels et al teach monoclonal antibodies against the exctracellular domain of the C-erbB-2 receptor, which is over expressed in a high percentage of primary breast and ovarian carcinomas. Wels et al teach that the antibody molecules are genetically engineered to minimize their size and to allow for functional modification. Wel et al teach that the cDNA sequences corresponding to the variable domains of one monoclonal antibody (FRP5) were molecularly cloned and joined by a short linker and the resulting single chain antibody molecule (scFv) was expressed in bacteria and purified (see abstract, lines 5-12). Wel et al teach that a major problem of the mouse monoclonal antibody is the immunogenicity of mouse antibody in humans (see page 1,

left column, lines 19-21). Wels et al. do not teach nucleic acids encoding human c-erbB-2 antibodies or human C6 or C6.5 antibodies. Wels et al do not teach to make antibodies which bind SK-BR-3 cells with a K_d less than about $1.6x10^{-8}$.

Marks et al teach that for serotherapy, monoclonal antibodies would ideally be of human origin. Marker et al teach making of human antibodies to specific antigens in a phage display system, which allows human antibodies to be made directly in vitro without prior immunization (see abstract). The resultant antibodies are quoted to have affinities in the range of 10^{-8}M.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make nucleic acids encoding a human single chain anti-c-erbB-2 antibody from the human c-erbB-2 antibody of US patent 6,165,464 and to express these antibodies in cells as taught by Wels et al., or to make nucleic acids encoding a human single chain anti c-erbB2 antibody with higher affinities from the human c-erbB-2 antibody of US patent 6,165,464 as taught by Marks et al. Moreover, one of ordinary skill in the art would have a reasonable expectation of success to make nucleic acids encoding a human single chain anti-c-erbB2 antibody because Wels et al. and Marks et al successfully teach how to make single chain antibody and other antibody fragments. Additionally, one would have been motivated to do so in view of the fact that c-34bB-2 is over expressed in tumor cells and can serve as a target for anti-tumor therapy, and also because that such antibodies could be used to inhibit tumor growth as taught by US patent NO: 6,165,464 and Wels et al.

Conclusion

20. No claims are allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CHRISTOPHER YAEN
PATENT EXAMINER

Hong Sang
Art Unit: 1643
September 1, 2005